

Application No. 10/006,290

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Docket No. 506612000100

REMARKS**RECEIVED
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Claims 55 to 72 are pending and under examination in the present application. Claims 56 to 65 have been withdrawn from consideration as being drawn to a nonelected invention. Claims 55 and 66-62 have been rejected.

Claim 55 has been amended to recite a method for diagnosis or monitoring transplant rejection by "determining the RNA level transcribed from a DNA". Claim 67 has been cancelled to avoid redundancy and claims 68-71 have been amended to make them consistent with the amended claims. Support for these amendments can be found in the specification, for example, at page 29, second full paragraph. Thus, there is no issue of new matter with respect to the amended claims.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the cancelled or unamended claims.

Applicants request reconsideration of the pending claims in view of the following remarks.

I. Elections/Restrictions

Applicants affirm the election with traverse of Group V, which corresponds to claim 55 and the further election of SEQ ID NO: 4758. Applicants acknowledge that the Examiner has made the restriction requirement final and that a complete reply to a final rejection includes cancellation of the nonelected claims. However, Applicants filed a Petition from a Restriction Requirement under 37 C.F.R. 1.144 on October 12, 2006 (a copy of which is enclosed herewith) and are awaiting a decision before cancelling the nonelected claims.

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II. Objections to the Specification**A. Title of Invention**

The Office Action objects to the title of the invention as not being descriptive. Applicants respectfully traverse this rejection. However, in order to expedite prosecution, Applicants have amended the Title to "Methods for Diagnosing and Monitoring Transplant Rejection using Leukocyte Expression Profiling" in order to more clearly reflect the claimed embodiment of the invention and thus request withdrawal of the objection.

B. Abstract of Invention

The Office Action objects to the abstract of the invention as not reflecting the claimed invention. Applicants respectfully traverse this rejection. However, in order to expedite prosecution, Applicants have amended the Abstract to more clearly reflect the claimed embodiment of the invention and thus request withdrawal of the objection.

III. New Matter Rejection

The Office Action rejects claims 55 to 72 filed in the November 22, 2005 amendment as being new matter prohibited under 35 U.S.C. § 132(a). Specifically, the Office Action alleges that "a review of the specification, including the 23 examples provided, fails to teach the claimed invention."

Applicants respectfully traverse this rejection and its supporting remarks. Applicants are permitted to add by amendment material found in the original specification, claims, or drawings. Applicants respectfully assert that support for claims 55-72 as filed in the November 22, 2005 amendment and as amended herewith is present throughout the originally filed application, in both the originally filed claims and the specification.

Claims 55-72, which are drawn to methods of diagnosing or monitoring transplant rejection, were added as part of a response electing Group V, which the Examiner himself characterizes in the Restriction Requirement as being "drawn to a method for *diagnosing a disease*,

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classified in class 435, subclass 6" (Restriction Requirement, page 2). Furthermore, original claim 40, the representative claim for Group V, explicitly provides support for claims 55-72, reciting "a method for *diagnosing a disease* comprising obtaining a leukocyte sample from an individual, contacting said leukocyte sample with the *gene expression system of claim 31* and comparing the expression of the gene with a molecular signature indicative of the presence or absence of said disease." The referenced claim 31 is drawn to a system comprising "an isolated DNA molecule detecting expression of a gene wherein said gene is selected from the group of genes corresponding to the oligonucleotides depicted in SEQ ID NO: 1 - SEQ ID NO: 8143," thus providing support for the specific sequences recited in claim 55.

Additional support for these claims is found in the specification itself. For example, on pages 55-58, the specification provides detailed description of the use of diagnostic nucleotide sets for diagnosis and monitoring of transplant rejection for various organs, including heart, kidney, bone marrow, liver, *etc.* Finally, pages 28 to 40 of the specification describe the various methods for detection of expression levels that are recited in the dependent claims.

Thus, both the originally filed claims and specification provide support for claims 55-72 as filed in the November 22, 2005 amendment and as amended herewith. Applicants therefore respectfully assert that no new matter has been added and request withdrawal of the objection.

IV. Rejection under 35 U.S.C. § 112, second paragraph

The Office Action rejects claim 55 under 35 U.S.C. § 112, second paragraph, as being indefinite for reciting "determining the expression level of a nucleic acid". Specifically, the Office Action alleges that while a nucleic acid may well encode a protein, the nucleic acid is not expressed and further, the protein is being expressed with the DNA being transcribed to mRNA and the mRNA subsequently being translated into a protein.

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Applicants have amended claim 55 to recite "determining the RNA level transcribed from a DNA" Therefore, the amended claims are definite and Applicants thus request withdrawal of the rejection.

V. Rejection under 35 U.S.C. § 112, first paragraph, Written Description

The Office Action maintains the rejection of claims 55 and 66-72 under 35 U.S.C. § 112, first paragraph, for failure to comply with the written description requirement. The Examiner finds Applicants' arguments that written description support is found in the Summary of the Invention and the Sequence Listing to be unpersuasive. Specifically, the Examiner alleges that Examples 11 and 12 come closest to the claimed method but only disclose diagnostic gene sets useful for diagnosis and treatment of allograft rejection, while the claims also encompass the actual expression of encoded protein.

To the extent the rejection applies to the newly amended claims, Applicants respectfully traverse the rejection and its supporting remarks. In order to satisfy the written description requirement, all that is required is that each claim limitation be either expressly, implicitly, or inherently supported in the specification. MPEP §2163(II)(A)(3)(b).

A. Written Description in Summary of Invention

As filed, the specification provides explicit description of each and every limitation of the newly amended claims. As noted in our previous response, this description begins in the Summary of the Invention section which provides a general description of the claims. Specifically, in this section the invention is described as being directed to methods of diagnosing or monitoring diseases by obtaining leukocyte samples and detecting expression of a diagnostic nucleotide set (p. 8, paragraphs 31 to 35). The contents of these diagnostic nucleotide sets are described on page 5, paragraph 15, as having "at least one oligonucleotide wherein the oligonucleotide has a sequence selected from those sequences listed in Table 2, Table 3, or the Sequence Listing which is differentially expressed in leukocytes in an individual with at least one disease criterion for a disease selected from Table 1 as compared to leukocytes from an individual without at least one

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disease criterion." By further referring to Table 2 and the sequence listing, one of skill would understand which DNAs are detected in methods of this invention, including elected SEQ ID NO: 4758. Finally, by referring to Table 1 (p. 183), one of skill would understand that methods of this invention can be used to detect transplant rejection. Thus, simply by referring to the Summary of the Invention and the referenced tables and sequence listing, one of skill would understand that the method of the invention involves determination of the RNA level transcribed from DNA to diagnose or monitor transplant rejection.

B. Written Description in Other Parts of the Specification

Further description of each limitation of the methods of this invention is provided in the rest of the specification.

The use of determination of RNA level transcribed from DNA to diagnose or monitor disease is generally described, for example, in the section of the specification entitled "Gene expression systems of the invention," which describes systems having oligonucleotides to detect "expression of a gene that is differentially expressed in leukocytes" and further notes that "such sequences may be predictive of a disease state." (p. 16). Additionally, in the section entitled "Methods of using diagnostic nucleotide sets" (p. 71), the specification describes the invention as providing "methods of using the diagnostic nucleotide sets to: *diagnose disease; assess severity of disease; predict future occurrence of disease; predict future complications of disease; determine disease prognosis; evaluate the patient's risk, or "stratify" a group of patients; assess response to current drug therapy; assess response to current non-pharmacological therapy; determine the most appropriate medication or treatment for the patient; predict whether a patient is likely to respond to a particular drug; and determine most appropriate additional diagnostic testing for the patient, among other clinically and epidemiologically relevant applications.*"

The identity of the DNA which can be used to diagnose or monitor disease is described, for example, in the section entitled "Diagnostic oligonucleotides of the invention," which describes diagnostic oligonucleotide sets containing "members of the leukocyte candidate library listed in

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Table 2, Table 3, and in the Sequence Listing, for which a correlation exists between the health status of an individual, and the individual's expression of RNA or protein products corresponding to the nucleotide sequences" or "oligonucleotide sequences listed in Table 2 or Table 3 or the Sequence Listing which are differentially expressed in leukocytes in an individual with at least one disease criterion for at least one leukocyte-implicated disease relative to the expression in individual without the at least one disease criterion, wherein expression of the two or more nucleotide sequences is correlated with at least one disease criterion." As discussed in the previous response, both Table 2 and the Sequence listing identify SEQ ID NO: 4758, the elected sequence, as well as the other presently nonelected sequences.

Methods for determining the RNA level transcribed from DNA to diagnose or monitor disease are described, for example, in the sections of the specification entitled "Obtaining DNA, RNA and protein samples for expression profiling" (p. 29) and "Methods for obtaining expression data" (p.33).

Finally, the use of RNA level transcribed from DNA to diagnose or monitor transplant rejection is also described throughout the specification. For example, the section entitled "Selected diseases" states "in principle, *diagnostic nucleotide sets* of the invention may be developed and applied to essentially any disease, or disease criterion, as long as at least one subset of nucleotide sequences is differentially expressed in samples derived from one or more individuals with a disease criteria or disease and one or more individuals without the disease criteria or disease ..." and goes on to describe on pages 56 to 58 the use of these diagnostic nucleotide sets for diagnosis of "transplant rejection and success."

Thus, given the description in the Summary of the Invention as well as the rest of the specification, one of skill would readily have recognized that Applicants had possession of the claimed invention. All limitations of the presently pending claims are described in the Summary of the Invention. Furthermore, additional description of each claim limitation is provided throughout the specification, in particular, in the sections entitled "Gene expression systems of the invention,"

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"Diagnostic oligonucleotides of the invention," "Methods of using diagnostic oligonucleotide sets of the invention," and "Selected diseases".

In view of the above, Applicants thus respectfully submit that the presently pending claims satisfy the written description requirement and request withdrawal of the rejection.

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Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 506612000100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 19, 2006

Respectfully submitted,

By Michael R. Ward
Michael R. Ward
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425 Market Street
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ATTORNEY DOCKET NO.: 506612000100 SERIAL NO.: 10/008,390 FILING DATE: October 12, 2006 INVENTOR(S): JAY WOELGEMUTH et al. TITLE: LEUKOCYTE EXPRESSION PROFILING			
Papers attached herewith: 1. Transmittal - 1 page 2. Petition From Restriction Requirement - 6 pages			
PAGE 10 * RCVD AT 10/19/2006 9:04:32 PM [Eastern Daylight Time] * SVR:USPTO-EFXXRF-5/14 * DNIS:2738300 * CSID:415 2687522 * DURATION (mm-ss):06-32			

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TRANSMITTAL FORM (to be used for all correspondence after initial filing)		Application Number	10/006,290
		Filing Date	October 22, 2001
		First Named Inventor	Jay WOHLGEMUTH, M.D.
		Art Unit	1634
		Examiner Name	B. L. Sisson
Total Number of Pages in This Submission	7	Attorney Docket Number	506612000100

ENCLOSURES (Check all that apply)

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP (Customer No. 20872)		
Signature	<i>Michael R. Ward</i>		
Printed name	Michael R. Ward		
Date	10/12/06	Reg. No.	38,651

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Dated: 10/12/06

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(Victoria A. Wilson)

sf-2207005

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Docket No.: 506612000100
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jay WOHLGEMUTH et al.

Application No.: 10/006,290

Filed: October 22, 2001

For: LEUKOCYTE EXPRESSION PROFILING

Confirmation No.: 8497

Art Unit: 1634

Examiner: B. L. Sisson

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PETITION FROM RESTRICTION REQUIREMENT

MS Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby petition the Commissioner to review the requirement for restriction in the above referenced application, as mailed September 23, 2005, and made "Final" in the Office Action mailed February 13, 2006. Specifically, Applicants request reconsideration of the restriction as applied to the ten (10) nucleic acid sequences recited in the claims of Group V.

Since Applicants made an election with traverse of Group V and SEQ ID NO: 4758 and requested reconsideration of the restriction requirement on November 22, 2005, Applicants have satisfied the statutory requirements for filing the instant petition.

I. Background to Petition

A restriction into eight (8) groups of claims was mailed September 23, 2005. In the restriction, the Examiner also articulated a "Sequence Restriction Requirement Applicable to Groups I-VII," requiring that Applicants elect a single sequence. As support for the rejection, the Examiner cited MPEP § 803.04, presumably for its characterization of nucleotide sequences

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encoding different proteins as structurally distinct chemical compounds and the categorization of such sequences as "independent and distinct inventions within the meaning of 35 U.S.C. § 121."

Applicants respectfully disagree with the restriction requirement.

II. There is no serious burden on the Examiner

The Examiner appears to believe that a restriction requirement is proper simply because there are independent or distinct inventions. However, this is simply not the law. A restriction requirement is only proper when the inventions are independent or distinct and there would be a serious burden on the Examiner if restriction was not required. MPEP § 803(I).

The sequences at issue are short 50-mer sequences set forth in Table 8. In view of the existing widely available resources for sequence searching, a search of 10 such nucleic acids cannot be considered to constitute a serious burden. In order to search for relevant prior art, the Examiner merely needs to copy the sequences in the present claims, paste them into an Internet database, and select the search button or hit the "enter" key.

Furthermore, under section 803.02 of the MPEP, if the members of a Markush group can be examined without serious burden, the Examiner must examine all members even though they may be directed to independent and distinct inventions. A limited number of Markush members or a close relation between Markush members can support a finding that a search can be made without serious burden. MPEP § 803.02. Present claim 55 is directed to a Markush group of 10 nucleic acid sequences. Although the MPEP fails to offer guidelines as to what size of Markush group is small enough to avoid incurring a serious burden on the PTO, surely it is safe to assume that 10 nucleic acid sequences, which has been deemed to be a generally reasonable number for examination purposes in MPEP §803.04, would also be small enough to satisfy the Markush group "undue burden" test for a restriction requirement.

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Since the Examiner faces no serious burden when examining the ten nucleic acid sequences, Applicants respectfully submit that the restriction requirement is improper and request withdrawal of the requirement.

III. The burden on Applicants and society far exceeds the burden on the PTO

As made clear by § 803.04, the section of the MPEP setting forth special rules for restriction of nucleotide sequences, the burden on Applicants should also be considered when determining whether to issue a restriction requirement, particularly with respect to biotechnology companies.

The burdens of restricting the pending claims to a single sequence are particularly acute in this case. Applicants not only face the long development times faced by all biotechnology companies, but also work at a small start-up company with limited resources. The Examiner's maintenance of the restriction requirement will force Applicants to incur the expense of filing nine (9) additional divisional applications, each of which will cost approximately \$10,000 to prepare, file and prosecute. The initial cost of filing the application will be further compounded by the additional maintenance and docketing costs for each application. All of these additional costs, which are a direct result of the restriction requirement, will place a severe financial burden on Applicants.

Given the limited resources of Applicants, such a financial burden will have substantial effects on the company, potentially forcing the company to downsize and limiting its ability to serve society by practicing its invention. Applicants' claimed invention is a method for monitoring or diagnosing transplant rejection by detecting the expression level of certain nucleic acids. A biopsy, the traditional method for detection of transplant rejection, is time-consuming, painful, and can involve the added risks of infection, organ damage and organ puncture. With the present invention, it is no longer necessary to subject transplant patients to multiple biopsies. Applicants' Allomap™ molecular expression test, an embodiment of this invention, is currently used to analyze samples from over 20 medical centers.

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In addition to imposing significant financial costs, maintenance of the restriction requirement will also impair outside investment in the company, an essential source of working capital for small start-up companies like the one at which Applicants work. Parties will not invest in a company unless they believe they will obtain a fair return on their investment. A patent allows Applicants to reassure investors that they will have a period of exclusivity during which they will enjoy the unparalleled competitive advantage of being the only party on the market with a particular invention.

Finally, in addition to the burden on Applicants themselves, the Examiner's insistence on maintaining the restriction requirement also places a significant burden on society. As mentioned previously, the financial pressures on Applicants will limit availability of this invention to society. Furthermore, by restricting the present application so that a single sequence is the subject of each application, the Examiner is burdening the PTO with examination of ten applications instead of a single application. This duplication of effort wastes the time of the PTO's employees, who we understand are already burdened by the increasing number of applications being filed. **If the PTO cannot handle its existing workload, why force applicants to file nine divisional applications?**

As described above, if the restriction requirement is withdrawn, the Examiner simply needs to copy the text of each of the nine remaining sequences provided in the claims and perform an Internet search in order to examine the sequences of the claims. In light of the significantly larger burdens on Applicants and society imposed by the restriction requirement, Applicants respectfully request that the restriction requirement be withdrawn.

IV. Under the current MPEP guidelines relating to restriction of nucleotide sequences, ten sequences should be examined

In the case of nucleotide sequences, the PTO has officially recognized that "normally ten sequences" [can] ... constitute a reasonable number for examination purposes," and explicitly states that its rationale is to aid the biotechnology industry. MPEP § 803.04. The MPEP presents this as a general rule, conceding only that in some exceptional cases will the complex nature of the claimed material require that the reasonable number of sequences to be selected to be less than ten. MPEP §

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803.04. As an example of what type of invention is considered to have a complex nature, the MPEP cites a claimed protein amino acid sequence reciting three dimensional folds.

The presently claimed invention is a method for diagnosing or monitoring transplant rejection in a patient comprising determining the expression level of a nucleic acid, where the nucleic acid comprises a nucleic acid selected from the group consisting of SEQ ID NO: 3702, SEQ ID NO: 2073, SEQ ID NO: 213, SEQ ID NO: 3028, SEQ ID NO: 4758, SEQ ID NO: 6299, SEQ ID NO: 832, SEQ ID NO: 2143, SEQ ID NO: 3651, and SEQ ID NO: 3750. The claimed sequences are nucleic acids without any particular structural limitations beyond the nucleotide sequence. By any measure, it is difficult to see how one could consider such sequences to have a complex nature that would require the number of sequences to be limited to less than ten.

Furthermore, the PTO has previously found claimed sequences having a nature similar to those in the present case to be sufficiently simple to be examined in a single application. Currently pending application 10/325,899 assigned to Expression Diagnostics, Inc., has pending claims directed to ten nucleic acid sequences undergoing active prosecution. The present Examiner has failed to offer any reason why the sequences of 10/325,899 are suitable for examination in a single application, while the presently claimed sequences are not.

Thus, given the special MPEP guidelines relating to examination of nucleotide sequence claims, the presently claimed ten nucleic acid sequences should be rejoined and subject to examination.

V. Conclusion

In view of the above, Applicants respectfully assert that all ten sequences in the Markush group cited in claim 55 should be examined together. Given the existing Internet databases for sequence searching, examination of all 10 sequences in a single application will not constitute a serious burden on the Examiner. Moreover, this burden is very slight compared to the burden placed on Applicants and society by filing nine additional applications. Finally, the PTO itself has recognized that ten sequences will normally constitute a reasonable number of sequences for

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examination purposes and in particular, has recognized this for sequences having a structure similar to those under examination in this application. Accordingly, Applicants request withdrawal of the restriction requirement and joinder of all ten sequences listed in claim 55 as amended in the response filed May 15, 2006.

Applicants have timely traversed the restriction requirement in this application. Applicants have submitted this petition within the time limits imposed by 37 C.F.R § 1.144. We have not identified a fee associated with this petition. If this is incorrect, the Commissioner is authorized to charge the cost of such fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 506612000100.

Dated: 10/19/2006

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